

5.2.4

Anti-Diuretic Hormone (ADH)

Watch the video [Diuretics Part 2 - Loops, Thiazides, K+ Sparing, ADH Antagonists](#) from 7:08 minutes to 8:50 minutes. It is recommended that you take notes that will help you answer the questions on the study guide.

Antidiuretic hormone (ADH), also known as **vasopressin**, is made by the supraoptic and paraventricular nuclei of the hypothalamus and then transported to the posterior pituitary gland through the hypothalamo-hypophyseal tract and stored until the body needs it. Increased osmolality of the blood, decreased blood pressure, and angiotensin II all act to increase the release of ADH from the posterior pituitary.

ADH travels through systemic circulation until it reaches the collecting ducts of the kidney. ADH will bind to a **V2 receptor** on the basolateral membrane of the nephron. This binding activates a G protein complex which in turn causes the activation of adenylate cyclase that converts ATP into cAMP. cAMP activates protein kinase A (PKA) which phosphorylates proteins that cause intracellular vesicles containing aquaporin 2 channels to translocate to the apical membrane of the cell. Once these aquaporin 2 channels are on the apical membrane, water can freely enter the cell from the filtrate and then pass through constitutively open aquaporin 3 and 4 channels on the basolateral membrane into the blood. Through this chain of events, ADH acts to increase water retention and blood volume. For this reason, V2 receptor antagonists like conivaptan (Vaprisol) that increase urine output are useful in the treatment of edema seen in heart failure.

ADH, also stimulates vasoconstriction via binding and activation of V1a receptors expressed on vascular smooth muscle cells. Interestingly, ADH also binds V1b (same as V3) receptors found mainly in the anterior pituitary which stimulates ACTH secretion.

Diabetes Insipidus (DI)

Diabetes insipidus (DI) is caused by an insufficiency of ADH or a lack of response to it. Common manifestations include polyuria, polydipsia, hypernatremia, and hyperosmolality. Diabetes insipidus is very different from diabetes mellitus, which is an issue with insulin. An explanation of the meaning of their names may help you differentiate between them. Diabetes insipidus and diabetes mellitus were named anciently. "Diabetes" in Latin means "to pass through" and often refers to increased urine volume. "Insipidus" in Latin means "tasteless," while "mellitus" means "sweet." Combined, "diabetes insipidus" refers to a high volume of tasteless urine. In comparison, "diabetes mellitus" refers to a high volume of sweet tasting urine. The sweet taste observed with this disease is due to excess glucose that is often excreted in the urine. In the evaluation of DI, it is important to distinguish DI from other polyuric states such as diabetes mellitus and psychogenic polydipsia (which we will study in a moment).

There are two types of diabetes insipidus that can be differentiated by where the problem is taking place:

1. **Neurogenic DI** is characterized by a problem with the brain such as trauma or stroke that causes a decreased release of ADH. Treatment of a milder form of neurogenic DI could be ingesting excess water. **Desmopressin acetate (DDAVP)** is a synthetic vasopressin analog available in an oral form or nasal spray for more severe cases of neurogenic DI.
2. **Nephrogenic DI** is characterized by a problem with the kidney and how it responds to ADH. Patients with nephrogenic DI commonly have a V2 receptor malfunction. Congenital nephrogenic DI is present at birth and may be caused by defective V2 receptors or defective aquaporin channels. Pyelonephritis and polycystic kidney disease may also lead to nephrogenic DI. For nephrogenic DI, it is important to first address the underlying disorder.

Interestingly, both neurogenic and nephrogenic forms of DI respond to thiazide diuretics like hydrochlorothiazide. Normally thiazide diuretics increase urine volume, but with DI they can cause a paradoxical decrease in urine volume. As we have mentioned, diabetes insipidus causes excessive water loss. This water loss results in higher concentrations of Na^+ in the blood and hypernatremia can result. Hypernatremia increases blood volume by stimulating thirst (which leads to drinking more water) and pulling water away from body tissues so fluid shifts into circulation. This extra water in the blood will be excreted by the kidneys, increases urine volume, and diabetes insipidus continues. Thiazide diuretics help with DI because they block the uptake of sodium in the distal convoluted tubule. The decreased sodium levels results in decreased GFR via paracrine signals from the macula densa cells (recall that macula densa cells sense sodium concentration and regulate GFR accordingly) and contributes to decreased urine production. It has also been observed that thiazide diuretics induce increased water and sodium reabsorption by the proximal convoluted tubule (due to hypernatremia) which also minimizes urine production.

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

Syndrome of inappropriate antidiuretic hormone (SIADH) is characterized by excessive ADH release, even if serum osmolality is already low. The excess secretion of ADH observed with SIADH may be from the normal hypothalamic source, but the most common cause is ectopic production of ADH by tumors in various locations. Some of these locations include the lung, pancreas, duodenum, prostate, bladder, and the brain. Leukemia and lymphoma cancers can also produce ADH. ADH is increased in individuals experiencing trauma, stress, and illness and can cause symptoms of SIADH in severe cases. These types of patients can include those with various pulmonary disorders such as tuberculosis, asthma, and cystic fibrosis. Patients requiring mechanical ventilation also may have an increase in ADH. CNS disorders such as hydrocephalus, head injuries, meningitis, and encephalitis can also cause SIADH. Any surgery may also elicit a temporary rise in ADH and is believed to be due to fluid and volume changes. Medications including narcotics (morphine), nicotine, NSAIDs, and general anesthetics can all increase ADH as well.

Due to excessive ADH-induced water retention, SIADH causes dilutional hyponatremia if water intake exceeds the reduced urine output. With all the retention of water, sodium is diluted in the blood. Furthermore, the increased fluid in the vasculature (hypervolemic state) causes excess stress in the right atrium, leading to atrial natriuretic hormone (ANH) release. ANH acts on the kidney to cause natriuresis, further contributing to sodium loss and hyponatremia. A decreased hematocrit and decreased BUN level can also be seen in individuals with SIADH.

Fluid restriction is an important treatment for SIADH to correct hyponatremia. Furosemide (Lasix) is a loop diuretic that can help reduce the amount of free water in the body. Lithium and demeclocycline can also be given because they inhibit the action of ADH on the principle cells of the kidney so that less water will be reabsorbed. Sometimes a hypertonic sodium chloride solution (3%) is used to help with the hyponatremia. ADH receptor antagonists like conivaptan could also be a possible treatment option.

Other Conditions that Influence ADH Secretion and Thirst

There are several conditions that can cause increased ADH secretion and increased thirst. It is important to note that ADH does not induce thirst, but rather angiotensin II is the main hormone responsible for stimulating thirst. Heart failure and chronic kidney disease (CKD) where patients may have high levels of angiotensin II can cause thirst and increased ADH release. Drinking water combined with increased secretion of ADH will raise body water volume and reduce blood osmolality. Individuals taking anticholinergic drugs or antihistamines (that have crossover anticholinergic action) can

have increased thirst and increased ADH release as well. Cigarette smoking (specifically the nicotine) and treatment with opioids are known to increase the release of ADH and thus increase water retention. Alcohol is known for the opposite effect where it decreases ADH release. This results in more body water being lost in the urine, which explains why **polydipsia** (increased thirst) often accompanies drinking alcohol.

Psychogenic polydipsia is compulsive water drinking independent of physiological stimuli to drink that is seen in patients with psychiatric disorders, most commonly schizophrenia. This compulsive desire to drink is not necessarily due to high serum osmolality causing increased ADH secretion. Indeed, enough water may be consumed by these individuals to reduce serum osmolality (which could actually decrease ADH secretion) and they still may have thirst.



This content is provided to you freely by BYU-I Books.

Access it online or download it at

https://books.byui.edu/bio_381_pathophysiol/524_anti_diuretic_h.

